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(54) Title: CHROMIUM PICOLINATE COMPOSITIONS AND USES THEREOF

(57) Abstract

Compositions comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin–containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid, or both, and at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin–containing herb. The compositions may be enteric–coated. The compositions are useful for supplementing dietary chromium, lowering blood glucose levels, lowering serum lipid levels and increasing lean body mass.

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CHROMIUM PICOLINATE COMPOSITIONS AND USES THEREOF

Field of the Invention

The present invention relates to compositions comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid, or both, and at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, and uses of these compositions in lowering blood glucose levels, increasing lean body mass and lowering blood serum lipid levels.

Background of the Invention

Chromium is a nutritionally essential trace element. The essentiality of chromium in the diet was established in 1959 by Schwartz, as cited in *Present Knowledge in Nutrition*, page 571, fifth edition (1984, the Nutrition Foundation, Washington, DC). Chromium depletion is characterized by the disturbance of glucose, lipid and protein metabolism and by a shortened lifespan. Chromium is essential for optimal insulin activity in all known insulin-dependent systems (Boyle et al., *Southern Med. J.* **70**:1449-1453, 1977). Insufficient dietary chromium has been linked to both maturity-onset diabetes and to cardiovascular disease.

The principle energy sources for the body are glucose and fatty acids. Chromium depletion results in biologically ineffective insulin and compromised glucose metabolism. Under these conditions, the body must rely primarily on lipid metabolism to meet its energy requirements, resulting in the production of excessive amounts of acetyl-CoA and ketone bodies. Some of the documented acetyl-CoA is converted to increased cholesterol biosynthesis, resulting in hypercholesterolemia. Diabetes mellitus is characterized in large part by glycosuria, hypercholesterolemia, and often ketoacidosis. The accelerated atherosclerotic process seen in diabetics is associated with hypercholesterolemia (Boyle et al., *supra.*).

Dietary supplementation of chromium to normal individuals has been reported to lead to improvements in glucose tolerance, serum lipid concentrations, including high-density lipoprotein cholesterol, insulin and insulin binding (Anderson, *Clin. Psychol. Biochem.* **4**:31-41, 1986). Supplemental chromium in the trivalent form, e.g. chromic chloride, is associated with improvements of risk factors associated with adult-onset (Type II) diabetes and cardiovascular disease.

Chromium functions as a cofactor for insulin. It binds to the insulin receptor and potentiates many, and perhaps all, of its functions (Boyle et al., *supra.*). These functions include, but are not limited to, the regulation of carbohydrate and lipid metabolism. (*Present Knowledge in Nutrition*, *supra*, at p. 573-577). The introduction of inorganic chromium compounds *per se* into individuals is not particularly beneficial. Chromium must be converted endogenously into an organic complex or must be consumed as a biologically active molecule. Only about 0.5% of ingested inorganic chromium is assimilated into the body (*Recommended Daily Allowances*, Ninth Revised Edition, The National Academy of Sciences, page 160, 1980). Only 1-2% of most organic compounds is assimilated into the body.

U.S. Patent No. Re. 33,988 discloses that when selected essential metals, including chromium, are administered to mammals as exogenously synthesized coordination complexes of picolinic acid, they are directly

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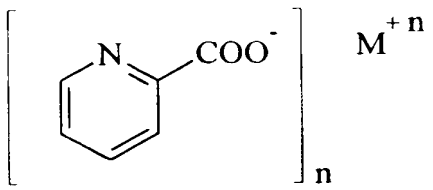
available for absorption without competition from other metals. This patent describes a composition and method for selectively supplementing the essential metals in the human diet and for facilitating absorption of these metals by intestinal cells. These complexes are safe, inexpensive, biocompatible and easy to produce. These exogenously synthesized essential metal coordination complexes of picolinic acid (pyridine-2-carboxylic acid) have the following structural formula:



wherein M represents the metallic cation and n is equal to the cation's valence. For example, when M is Cr and n=3, then the compound is chromic tripicolinate. Other chromium picolinates disclosed include chromic monopicolinate and chromic dipicolinate.

The U.S. Recommended Daily Intake (RDI) of chromium is 120 μg. U.S. Patent No. 5,087,623, the entire contents of which are hereby incorporated by reference, describes the administration of an effective amount of chromic tripicolinate for the treatment of adult-onset diabetes. International Patent Application No. WO96/35421 discloses the use of high doses of chromic tripicolinate (providing 1,000-10,000 μg chromium/day) for reducing hyperglycemia and stabilizing the level of serum glucose in humans with Type II diabetes. Allowed U.S. Patent Application Serial No. 08/908,819 discloses a chromic tripicolinate-biotin composition and its use in lowering blood glucose levels in humans with Type II diabetes.

U.S. Patent Nos. 5,087,623; 5,087,624; and 5,175,156, the entire contents of which are hereby incorporated by reference, disclose the use of chromium tripicolinate for supplementing dietary chromium, reducing hyperglycemia and stabilizing serum glucose, increasing lean body mass and reducing body fat, and controlling blood serum lipid levels, including the lowering of undesirably high blood serum LDL-cholesterol levels and the raising of blood serum HDL-cholesterol levels. U.S. Patent Nos. 4,954,492 and 5,194,615, the entire contents of which are hereby incorporated by reference, describe a related complex, chromic polynicotinate, which is also used for supplementing dietary chromium and lowering serum lipid levels. Picolinic acid and nicotinic acid are position isomers having the following structures:

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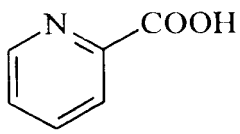
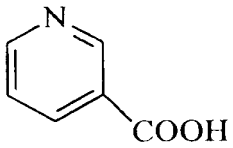


picolinic acid



nicotinic acid

Nicotinic acid and picolinic acid form coordination complexes with monovalent, divalent and trivalent metal ions and facilitate the absorption of these metals by transporting them across intestinal cells and into the bloodstream. Chromium absorption in rats following oral administration of $CrCl_3$ was facilitated by the non-steroidal anti-inflammatory drugs (NSAIDs) aspirin and indomethacin (Davis et al., *J. Nutrition Res.* **15**:202-210, 1995; Kamath et al., *J. Nutrition* **127**:478-482, 1997). These drugs inhibit the enzyme cyclooxygenase which converts arachidonic acid to various prostaglandins, resulting in inhibition of intestinal mucus formation and lowering of intestinal pH which facilitates chromium absorption.

The present invention provides improved chromic tripicolinate and chromic polynicotinate compositions which facilitate absorption of chromium and other endogenous or exogenous metals, for use in lowering blood glucose levels, serum lipid levels and increasing lean body mass.

Summary of the Invention

One embodiment of the present invention is a composition for supplementing dietary chromium and facilitating absorption of essential metals, the composition comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid, or both and at least one of a cyclooxygenase inhibitor, an acid, a mucolytic and a salicin-containing herb. Preferably, the cyclooxygenase inhibitor is aspirin, indomethacin, ibuprofen, acetaminophen, naproxen or other compound with cyclooxygenase inhibitor activity, e. g. vitamin E. In one aspect of this preferred embodiment, the mucolytic is guaifenesin. In another aspect of this preferred embodiment, the acid is ascorbic acid or citric acid. Advantageously, the formulation is a tablet, capsule or microbead. Preferably, the microbead is a sugar beadlet or microcrystalline cellulose beadlet and the composition is coated on the beadlet. In another aspect of this preferred embodiment, the chromic tripicolinate composition is enteric-coated.

The present invention also provides a method for supplementing dietary chromium in an individual, comprising orally administering to the individual a composition comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid, or both and at least one of a cyclooxygenase inhibitor, an acid, a mucolytic and a salicin-containing herb. In one aspect of this preferred embodiment, the formulation is a tablet, capsule or microbead. Preferably, the microbead is a sugar beadlet or microcrystalline cellulose

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beadlet and the composition is coated on the beadlet. In another aspect of this preferred embodiment, the chromic tripicolinate composition is enteric-coated.

Another embodiment of the invention is a method for reducing hyperglycemia and stabilizing serum glucose levels in an individual in need thereof, comprising orally administering to the individual an effective daily hyperglycemia-reducing amount of a composition comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid, or both and at least one of a cyclooxygenase inhibitor, an acid, a mucolytic and a salicin-containing herb. Advantageously, the composition is in the form of a tablet, capsule or microbead. Preferably the microbead is a sugar beadlet or microcrystalline cellulose beadlet and the composition is coated on the beadlet. In another aspect of this preferred embodiment, the chromic tripicolinate composition is enteric-coated.

Another embodiment of the invention is a method for increasing lean body mass and reducing body fat of an individual in need thereof, comprising orally administering to the individual an effective, lean body mass-increasing amount of a composition comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid, or both, and at least one of a cyclooxygenase inhibitor, an acid, a mucolytic and a salicin-containing herb. In one aspect of this preferred embodiment, the composition is in the form of a tablet, capsule or microbead. Preferably, the microbead is a sugar beadlet or microcrystalline cellulose beadlet and the composition is coated on the beadlet. In another aspect of this preferred embodiment, the chromic tripicolinate composition is enteric-coated.

The present invention also provides a method for reducing high levels of blood serum lipids in an individual in need thereof, comprising administering to the individual an effective blood serum lipid-reducing amount of a composition comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid, or both, and at least one of a cyclooxygenase inhibitor, an acid, a mucolytic and a salicin-containing herb. In one aspect of this preferred embodiment, the composition is in the form of a tablet, capsule or microbead. Preferably, the microbeac is a sugar beadlet or microcrystalline cellulose beadlet and the composition is coated on the beadlet. In another aspect of this preferred embodiment, the chromic tripicolinate composition is enteric-coated.

Detailed Description of the Preferred Embodiments

The present invention provides compositions comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid, or both and at least one of a cyclooxygenase (cox) inhibitor, acid, mucolytic and salicin-containing herb. In a preferred embodiment, the chromic tripicolinate is synthetic. The chromic tripicolinate facilitates absorption of chromium by intestinal cells. The additional picolinic acid

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and/or nicotinic acid in the composition facilitates absorption of other ingested chromium as well as other metals including, but not limited to, copper, iron, magnesium, manganese and zinc.

In another embodiment of the invention, the chromic tripicolinate compositions, either alone or in combination with additional nicotinic acid, picolinic acid, or nicotinic acid/picolinic acid, are provided in combination with at least one of a cox inhibitor, acid, mucolytic and salicin-containing herb. Cox inhibitors include, but are not limited to, aspirin (acetylsalicylic acid), other salicylates, or another NSAID such as indomethacin, ibuprofen, acetaminophen, naproxen or any compound capable of inhibiting the cyclooxygenase pathway leading to prostaglandin synthesis. This results in a decrease in intestinal mucus production and lower intestinal pH which facilitates absorption of the chromic tripicolinate compositions of the present invention. The oral compositions may further include mucolytics such as guaifenesin and the like, to inhibit intestinal mucus production, and/or acids such as ascorbic acid, citric acid and the like to lower intestinal pH. Inclusion of one or both of these compounds further enhances chromium absorption. There are two forms of cyclooxygenase (cox), cox1 and cox2, which differ in their sensitivity to inhibition by NSAIDs. The cox2 isozyme promotes prostaglandin formation at sites of inflammation, but not at other sites such as the gastrointestinal tract. In contrast, relatively selective inhibition of cox1 facilitates chromic tripicolinate and chromic polynicotinate absorption. Although the selective inhibition of cox1 is desirable, any inhibitor or cox1 or cox2 can be formulated with the chromic tripicolinate and chromic polynicotinate compositions of the invention. Cox inhibitors, acids and mucolytics may also be coadministered with the chromic tripicolinate and chromic polynicotinate compositions of the invention. The amount of these drugs formulated with or coadministered with the chromic tripicolinate and chromic polynicotinate compositions of the invention are as follows: cox inhibitors, between about 50 mg and 500 mg; mucolytics, between about 10 mg and 250 mg; and acids, between about 50 mg and about 1,000 mg.

The coadministration or formulation of salicylate-containing herbs with the chromic tripicolinate compositions of the invention is also contemplated. Class I herbs, as documented in the American Herbal Products Association's *Botanical Safety Handbook* (herbs that can be safely consumed when used appropriately), such as *Boswellia serrata* (frankincense), *Betula lenta* (sweet birch), *Betula pubescens* (white birch), *Filipendula ulmaria* (meadowsweet), *Gaultheria procumbens* (wintergreens), *Populus balsamifera* and *Populus jackii* (balm of Gilead), and *Salix alba* (white willow) are all salicin-containing plants with salicylate-like properties. These herbs suppress prostaglandin synthesis by cox inhibition, thereby improving absorption of the chromic tripicolinate compositions of the invention. These herbs are relatively free from gastric ulcerogenic effects (Singh et al., *Agents and Actions* 18:407-412, 1986). In addition, preclinical acute toxicity studies have shown that salicin-containing plants do not cause hematological disturbances (American Herbal Products Association, *Botanical Safety Handbook*, 1997).

The compounds and herbs described above all effect gut physiology by inhibiting prostaglandin synthesis, decreasing mucus production, and lowering gastrointestinal pH. The inclusion of these compounds, as well as an enteric coating, into the oral chromic tripicolinate compositions of the invention results in a multicomponent delivery system which allows delivery of these agents to the gastrointestinal tract where they work in concert to facilitate chromic tripicolinate absorption.

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The chromic tripicolinate compositions described above may also be coated with an enteric coating which prevents dissolution of the tablet, capsule or microbead in the acidic environment of the stomach. Instead, this coating dissolves in the small intestine at a more neutral pH. Because chromic tripicolinate may be more stable at this neutral pH than at the acidic pH of the stomach, enhanced absorption occurs because the chromic tripicolinate remains substantially intact until it reaches the small intestine. In addition, because chromic tripicolinate binds to food in the stomach which may inhibit its absorption by the small intestine, enteric coatings beneficially delay dissolution until the compound reaches the small intestine.. Such enteric coated compositions are described by Bauer et al., *Coated Pharmaceutical Dosage Forms: Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials*, CRC Press, Washington, DC, 1998, the entire contents of which are hereby incorporated by reference.

Thus, these compositions are readily absorbable forms of chromium which also facilitate absorption of other essential metals in the human diet. The chromic tripicolinate and chromic polynicotinate compositions of the invention have the same uses as described for chromic tripicolinate in U.S. Patent Nos. 5,087,623, 5,087,624, and 5,174,156, namely supplementing dietary chromium, lowering blood glucose levels in diabetics, lowering serum lipid levels and increasing lean body mass.

The synthesis and use of chromium picolinates is described in U.S. Patent Nos. Re 33,988 and 5,087,623. Chromic tripicolinate is available from health food stores, drug stores and other commercial sources, including Nutrition 21 (San Diego, CA). The synthesis and use of chromic polynicotinate is described in U.S. Patent No. 5,194,615. Picolinic acid and nicotinic acid are available from many commercial sources, including Sigma-Aldrich (St. Louis, MO) (picolinic acid; catalog No. P5503; nicotinic acid; catalog No. PN4126). The compositions of the present invention are prepared by incorporating the components into a pharmaceutically acceptable carrier, including but not limited to tablets, capsules and microbeads, preferably sugar beadlets or microcrystalline cellulose.

For oral administration, the components of the composition may be incorporated into a tablet, aqueous or oil suspension, dispersible powder or granule, microbead, emulsion, hard or soft capsule, syrup or elixir. These components may also be administered separately. Compositions may be prepared according to any method known in the art for the manufacture of pharmaceutically acceptable compositions and such compositions may contain one or more of the following agents: sweeteners, flavoring agents, coloring agents and preservatives. Tablets containing the active ingredients in admixture with non-toxic pharmaceutically acceptable excipients suitable for tablet manufacture are acceptable. "Pharmaceutically acceptable" means that the agent should be acceptable in the sense of being compatible with the other ingredients of the formulation (as well as non-injurious to the individual). Such excipients include inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, such as corn starch and alginic acid; binding agents such as starch, gelatin or acacia; and lubricating agents such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated with known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide

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a sustained action over a longer period of time. For example, a time delay material such as glyceryl monostearate or glyceryl stearate alone or with a wax may be employed.

Another embodiment of the present invention is a pharmaceutical composition comprising an enteric-coated chromic tripicolinate formulation. Any pharmaceutical formulation well known in the art can be coated with an enteric coating. In a preferred embodiment, the formulation is a tablet, capsule or microbead. The pharmaceutical formulation comprises chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid, or both, and at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions may contain the chromic tripicolinate or polynicotinate compositions of the invention in admixture with excipients for the manufacture of aqueous suspensions. Such excipients include suspending agents, dispersing or wetting agents, one or more preservatives, one or more coloring agents, one or more flavoring agents and one or more sweetening agents such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oil suspension may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agent, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by an added antioxidant such as ascorbic acid. Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

In a preferred embodiment, the components of the chromic tripicolinate compositions are coated onto microbeads. In a preferred embodiment, these microbeads are sugar beadlets of various sizes, also known as nonpareils, and are commercially available from, for example, SmithKline Beecham. If the microbeads are to be used to administer the compositions of the invention to diabetic patients, the administration of other types of microbeads, such as microcrystalline cellulose, is preferred. Microcrystalline cellulose is commercially available and can be processed into beadlets of various sizes by micronization, a technique well known in the art. The microbeads are essentially a carrier for the compositions of the invention. For a description of coated beadlets, see, for example, Carstensen, J. T., *Pharmaceutical Principles of solid Dosage Forms*, Technonic Publishing Co., Inc., Lancaster, PA, pp. 228-230, 1993, hereby incorporated by reference. Aqueous solutions containing the chromic tripicolinate or chromic polynicotinate and

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nicotinic acid and/or picolinic acid components of the composition are sprayed onto the microbeads by well known methods, by suspending the microbeads in an upcurrent of air and introducing a fine spray of the active ingredients which form a coating on the outside of the microbeads which is then allowed to dry. The desired components (e.g. chromic tripicolinate and ibuprofen) may be combined into the same solution or applied using separate solutions. Optionally, the coated microbeads can be further coated with a substance to protect the active ingredients coated onto the beads, such as latex. The microbeads may be placed in a capsule prior to administration. In another preferred embodiment, the capsule or the microbeads are coated with an enteric coating to delay dissolution until reaching the small intestine.

Typically, the chromic tripicolinate and chromic polynicotinate compositions of the invention provide between about 50 and 10,000 micrograms per day of chromium; preferably between about 100 and 2,000 micrograms per day; more preferably, between about 200 and 1,000 micrograms per day. In a preferred embodiment, the ratio of chromic tripicolinate to picolinic acid, nicotinic acid or picolinic acid/nicotinic acid ranges from about 10:1 to about 1:10 (w/w), more preferably from about 5:1 to about 1:5 (w/w).

It will be appreciated that although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

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WHAT IS CLAIMED IS:

1. A composition for supplementing dietary chromium and facilitating absorption of essential metals, said composition comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid or both and at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb.

2. The composition of Claim 1, wherein said composition is in the form of a tablet, capsule or microbead.

3. The composition of Claim 2, wherein the microbead is a sugar beadlet or microcrystalline cellulose beadlet and said composition is coated on said beadlet.

4. The composition of Claim 1, wherein said cyclooxygenase inhibitor is selected from the group consisting of aspirin, indomethacin, ibuprofen, acetaminophen and naproxen.

5. The composition of Claim 1, wherein said mucolytic is guaifenesin.

6. The composition of Claim 1, wherein said acid is ascorbic acid or citric acid.

7. The composition of Claim 1, wherein said salicin-containing herb is selected from the group consisting of *Boswellia serrata* (frankincense), *Betula lenta* (sweet birch), *Betula pubescens* (white birch), *Filipendula ulmaria* (meadowsweet), *Gaultheria procumbens* (wintergreens), *Populus balsamifera* , *Populus jackii* (balm of Gilead) and *Salix alba* (white willow).

8. The composition of Claim 1, wherein said composition is enteric-coated.

9. A method for supplementing dietary chromium in an individual, comprising orally administering to said individual a composition comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid or both and at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb.

10. The method of Claim 9, wherein said composition is in the form of a tablet, capsule or microbead.

11. The method of Claim 10, wherein the microbead is a sugar beadlet or microcrystalline cellulose beadlet and said composition is coated on said beadlet.

12. The method of Claim 9, wherein said composition is enteric-coated.

13. A method for reducing hyperglycemia and stabilizing serum glucose levels in an individual in need thereof, comprising orally administering to said individual an effective daily hyperglycemia-reducing amount of a composition comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid or both and at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb.

14. The method of Claim 13, wherein said composition is in the form of a tablet, capsule or microbead.

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15. The method of Claim 14, wherein said microbead is a sugar beadlet or microcrystalline cellulose beadlet and said composition is coated on said beadlet.

16. The method of Claim 13, wherein said composition is enteric-coated.

17. A method for increasing lean body mass and reducing body fat of an individual in need thereof, comprising orally administering to said individual an effective, lean body mass-increasing amount of a composition comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid or both and at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb.

18. The method of Claim 17, wherein said composition is in the form of a tablet, capsule or microbead.

19. The method of Claim 18, wherein said microbead is a sugar beadlet or microcrystalline cellulose beadlet and said composition is coated on said beadlet.

20. The method of Claim 17, wherein said composition is enteric-coated.

21. A method for reducing high levels of blood serum lipids in an individual in need thereof, comprising administering to said individual an effective blood serum lipid-reducing amount of a composition comprising chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid or both and at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb.

22. The method of Claim 21, wherein said composition is in the form of a tablet, capsule or microbead.

23. The method of Claim 22, wherein said microbead is a sugar beadlet or microcrystalline cellulose beadlet and said composition is coated on said beadlet.

24. The method of Claim 21, wherein said composition is enteric-coated.

25. Chromic tripicolinate in combination with at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, or in combination with picolinic acid, nicotinic acid, or both, or in combination with picolinic acid, nicotinic acid or both and at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb, for use in reducing hyperglycemia and stabilizing serum glucose levels, increasing lean body mass and reducing body fat, or reducing high levels of blood serum lipids.

SUBSTITUTE SHEET (RULE 26) WO 00/12094A1

AMENDED CLAIMS

[received by the International Bureau on 21 January 2000 (21.01.00); original claims 1-25 replaced by new claims 1-45 (3 pages)]

1. A composition for supplementing dietary chromium and facilitating absorption of essential metals, said composition comprising chromic tripicolinate in combination with a compound selected from the group consisting of a cyclooxygenase inhibitor other than acetylsalicylic acid, an acid other than acetylsalicylic acid, a mucolytic and salicin-containing herb, or chromic tripicolinate in combination with a compound selected from the group consisting of picolinic acid, nicotinic acid or both, or chromic tripicolinate in combination with a compound selected from the group consisting of picolinic acid, nicotinic acid or both and at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb.

2. The composition of Claim 1, wherein said composition is in the form of a tablet, capsule or microbead.

3. The composition of Claim 2, wherein said microbead is a sugar beadlet or microcrystalline cellulose beadlet and said composition is coated on said beadlet.

4. The composition of Claim 1, wherein said composition is enteric coated.

5. The composition of Claim 1, wherein said composition comprises chromic tripicolinate in combination with a cyclooxygenase inhibitor selected from the group consisting of indomethacin, ibuprofen, acetaminophen and naproxen.

6. The composition of Claim 1, wherein said composition comprises chromic tripicolinate in combination with an acid other than acetylsalicylic acid.

7. The composition of Claim 6, wherein said acid is ascorbic acid or citric acid.

8. The composition of Claim 1, wherein said composition comprises chromic tripicolinate in combination with a mucolytic.

9. The composition of Claim 8, wherein said mucolytic is guaifenesin.

10. The composition of Claim 1, wherein said composition comprises chromic tripicolinate in combination with a salicin-containing herb.

11. The composition of Claim 10, wherein said salicin-containing herb is selected from the group consisting of *Boswellia serrata* (frankincense), *Betula lenta* (sweet birch), *Betula pubescens* (white birch), *Filipendula ulmaria* (meadowsweet), *Gautheria procumbens* (wintergreens), *Polulus balsamifera*, *Populus jackii* (balm of gilead) and *Salix alba* (white willow).

12. The composition of Claim 1, wherein said composition comprises chromic tripicolinate in combination with picolinic acid.

13. The composition of Claim 12, further comprising nicotinic acid.

14. The composition of Claim 1, wherein said composition comprises chromic tripicolinate in combination with nicotinic acid.

15. The composition of Claims 12-14, further comprising a cyclooxygenase inhibitor.

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16. The composition of Claim 15, wherein said cyclooxygenase inhibitor is selected from the group consisting of indomethacin, ibuprofen, acetaminophen and naproxen.

17. The composition of Claims 12-14, further comprising an acid .

18. The composition of Claim 17, wherein said acid is ascorbic acid or citric acid.

19. The composition of Claims 12-14, further comprising a mucolytic.

20. The composition of Claim 19, wherein said mucolytic is guaifenesin.

21. The composition of Claims 12-14, further comprising a salicin-containing herb.

22. The composition of Claim 21, wherein said salicin-containing herb is selected from the group consisting of *Boswellia serrata* (frankincense), *Betula lenta* (sweet birch), *Betula pubescens* (white birch), *Filipendula ulmaria* (meadowsweet), *Gautheria procumbens* (wintergreens), *Polulus balsamifera, Populus jackii* (balm of gilead) and *Salix alba* (white willow).

23. A composition comprising chromic tripicolinate in combination with a compound selected from the group consisting of a cyclooxygenase inhibitor other than acetylsalicylic acid, an acid other than acetylsalicylic acid, a mucolytic and salicin-containing herb, or chromic tripicolinate in combination with a compound selected from the group consisting of picolinic acid, nicotinic acid or both, or chromic tripicolinate in combination with a compound selected from the group consisting of picolinic acid, nicotinic acid or both and at least one of a cyclooxygenase inhibitor, acid, mucolytic and salicin-containing herb for use in reducing hyperglycemia and stabilizing serum glucose levels, increasing lean body mass and reducing body fat, or reducing high levels of blood serum lipids.

24. The composition of Claim 23, wherein said composition comprises chromic tripicolinate in combination with a cyclooxygenase inhibitor selected from the group consisting of indomethacin, ibuprofen, acetaminophen and naproxen.

25. The composition of Claim 23, wherein said composition comprises chromic tripicolinate in combination with an acid other than acetylsalicylic acid.

26. The composition of Claim 25, wherein said acid is ascorbic acid or citric acid

27. The composition of Claim 23, wherein said composition comprises chromic tripicolinate in combination with a mucolytic.

28. The composition of Claim 27, wherein said mucolytic is guaifenesin.

29. The composition of Claim 23, wherein said composition comprises chromic tripicolinate in combination with a salicin-containing herb.

30. The composiiton of Claim 29, wherein said salicin-containing herb is selected from the group consisting of *Boswellia serrata* (frankincense), *Betula lenta* (sweet birch), *Betula pubescens* (white birch), *Filipendula ulmaria* (meadowsweet), *Gautheria procumbens* (wintergreens), *Polulus balsamifera, Populus jackii* (balm of gilead) and *Salix alba* (white willow).

31. The composition of Claim 23, wherein said composition comprises chromic tripicolinate in combination with picolinic acid.

32. The composition of Claim 31, wherein said composition further comprises nicotinic acid.

33. The composition of Claim 23, wherein said composition comprises chromic tripicolinate in combination with nicotinic acid.

34. The composition of Claims 31-33, further comprising a cyclooxygenase inhibitor.

35. The composition of Claim 34, wherein said cyclooxygenase inhibitor is selected from the group cnsisting of indomethacin, ibuprofen, acetaminophen and naproxen.

36. The composition of Claims 31-33, further comprising an acid .

37. The composition of Claim 36, wherein said acid is ascorbic acid or citric acid.

38. The composition of Claims 31-33, further comprising a mucolytic.

39. The composition of Claim 38, wherein said mucolytic is guaifenesin.

40. The composition of Claims 31-33, further comprising a salicin-containing herb.

41. The composition of Claim 40, wherein said salicin-containing herb is selected from the group consisting of *Boswellia serrata* (frankincense), *Betula lenta* (sweet birch), *Betula pubescens* (white birch), *Filipendula ulmaria* (meadowsweet), *Gautheria procumbens* (wintergreens), *Polulus balsamifera*, *Populus jackii* (balm of gilead) and *Salix alba* (white willow).

42. The composition of Claims 23-41 for use in reducing hyperglycemia and stabilizing serum glucose levels.

43. The composition of Claims 23-41 for use in increasing lean body mass and reducing body fat.

44. The composition of Claims 23-41 for use in reducing high levels of blood serum lipids.

45. The composition of Claims 23-41 for use in supplementing dietary chromium.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/14537

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/555

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 543 405 A (KEOWN WENDY J ET AL) 6 August 1996 (1996-08-06) claims 1,2,10 ---	1,2,4,9, 10,13, 14,17, 18,21, 22,25
X	US 5 175 156 A (BOYNTON HERB ET AL) 29 December 1992 (1992-12-29) column 14, line 19 - line 34; claims ---	1,2,6, 13,14, 17,18, 21,22,25
A	US 5 654 011 A (JACKSON SHERRY D ET AL) 5 August 1997 (1997-08-05) claims -----	1-25

☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 1999	24/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

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INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US 99/ 14537

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13-24
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 13-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-25 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-25 (all partially)

Present claims 1-25 relate to an extremely large number of possible compositions in view of the expressions used ("cyclooxygenase inhibitor"; "acid"; "salicin-containing herb"). These expressions also are insufficient for a full characterisation of the constituents. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the combinations claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the constituents specifically mentioned in claims 4-7, obvious variants thereof, and the general idea underlying the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PC., US 99/14537

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5543405 A	06-08-1996	AU 8085894 A	08-05-1995
		CA 2174422 A	27-04-1995
		EP 0724450 A	07-08-1996
		WO 9511034 A	27-04-1995
US 5175156 A	29-12-1992	US 5087623 A	11-02-1992
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US 5654011 A	05-08-1997	AU 3958797 A	20-02-1998
		CA 2261764 A	05-02-1998
		EP 0934060 A	11-08-1999
		WO 9804248 A	05-02-1998

Form PCT/ISA/210 (patent family annex) (July 1992)